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(71) Applicant *(for all designated States except US)*: DONG WHA PHARM. IND. CO., LTD. [KR/KR]; 5, Soonwha-dong, Joong-ku, Seoul 100-130 (KR).

(71)(72) Applicant and Inventor: SUH, Hong-Suk [KR/KR]; #1-502 Ilshin Apt., 1025, Kusuh 2-dong, Keumjung-ku, Pusan-si 609-312 (KR).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: RYU, Jae-Ha [KR/KR]; #603-803 Ssangyong Apt., Moonchon-maeul, 8, Jooyeop-dong, Ilsan-ku, Koyan-shi, Kyoungki 411-370 (KR). HAN, Yong-Nam [KR/KR]; 132, Imae-dong, Pundang-ku, Sungnam-si, Kyoungki-do 411-370 (KR). YOON, Sung-June [KR/KR]; 1420-11, Silim5-dong, Kwanak-ku, Seoul 151-015 (KR). KIM, Jong-Woo [KR/KR]; 1029, Bisan 3-dong, Dongan-ku, Anyang-shi, Kyoungki-do (KR).

(74) Agent: LEE, Won-Hee; Sungji Heights II, Suite 805, 642-16, Yoksam-dong, Kangnam-ku, Seoul 135-080 (KR).

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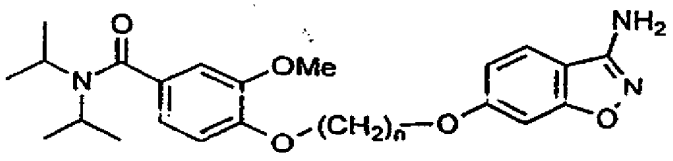
(54) Title: 3-AMINO-1,2-BENZOISOXAZOLE DERIVATIVES, PROCESS FOR PREPARATION, AND USE THEREOF

(57) Abstract

The present invention relates to a novel 3-amino-1,2-benzoisoxazole derivative, represented by formula (I),



(I)

LTB-4[leukotriene-B-4; 5(*S*),12(*R*)-dihydroxy-6,14-*cis*-8,10-*trans*-eicosatetraenoic acid] receptor antagonist, process for preparation thereof, and use thereof for LTB-4 receptor antagonist or therapeutics for osteoporosis. In formula (I) n is integer of 3-5.

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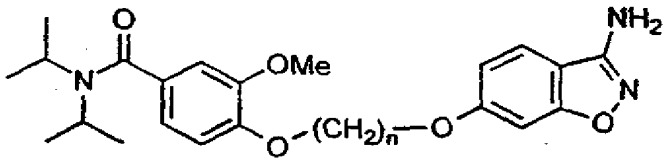
3-Amino-1,2-benzoisoxazole derivatives, process for preparation, and use thereof

Field of the Invention

The present invention relates to a novel 3-amino-1,2- benzoisoxazole derivatives, represented by Formula I, LTB-4[leukotriene-B-4; 5(*S*),12(*R*)-dihydroxy-6,14-*cis*-8,10-*trans*-eicosatetraenoic acid] receptor antagonist, process for preparation thereof, and use thereof for LTB-4 receptor antagonist or therapeutics for osteoporosis.

Formula I



(in which n is integer of 3-5.)

LTB-4, natural product, is metabolite of arachidonate, produced in the path way of 5-lipoxygenase [Ford-Hutchison, A. W. *et al.*, *Nature(London)*, *286*, 264-265, **1980**]. LTB-4 induces cohesion and degranulation of neutrophil, and promotes chemical taxis and locomotion of leukocyte, and LTB-4 contracts smooth muscle, and participate in the production of peroxide, and is also detected in a large amount at inflammatory lesions of

patient, such as psoriasis, enteritis, rheumatoid arthritis, bronchial asthma, and adult respiratory distress syndrome.

Compound for LTB-4 receptor antagonist, therefore, can be utilized effectively as inhibitor and treating medicine at the above mentioned disease(Clint, D. W. *et al.*, *J. Med. Chem.* *39*, 2629-2654, **1996**; Suh, H., USP 5,455,274, **1995**).

Usual LTB-4 receptor antagonists were SM-9064 (Namiki, M. *et al.*, *Biochem. Siophys. Res. Comm.* *138*, 540-546, **1986**); U-75302(Morris, J. *et al.*, *Tetrahedron Lett.* *29*, 143-146, **1988**); LY-255283(Herron, D.K. *et al.*, *FASEB J.* *2*, A1110, **1988**); SC-41930(Djuric, S. W. *et al.*, *J. Med. Chem.* *32*, 1145-1147, **1989**); LY-223982(Gapinski, D. M. *et al.*, *J. Med. Chem.* *33*, 2807-2813, **1990**); ONO-LB457(Konno, M. *et al.*, *Adv.Prostaglandin,Thromboxane Leukotriene Res.* *21*, 411-414, **1991**); CP-105696(Showell, H. J. *et al.*, *J. Pharmacol. Exper. Ther.* *273*, 176-184, **1995**); CGS-25019C (Morrissey, M. M., Suh, H. USP 5,451,700; Brooks, C. D. *et al.*, *J. Med. Chem.* *39*, 2629-2654, **1996**); and so on.

It has been reported that CGS-25019C, which is in the highest critical step, have toxicity to stimulate stomach and intestine among the usual antagonist. So, it is necessary to develop a novel LTB-4 receptor antagonist.

Bone maintain necessary bone mass and the structure

as a physical support of body, and play a important role as keeping the concentration of Ca^{2+}, etc. in blood as a stock of Ca^{2+} and so on.

Bone reporption and remodeling is continuously recycled, to carry out the above functions, and is in the dynamic state of metabolite with resorbing and remodeling of bone. When the remodeling of bone does not equilibrate the resorption of bone, the resorption is relatively superior to the remodeling of bone, and it causes the reduction of bone density and mass to osteoporosis, which is in the state of not maintaining of bony strength. Osteoporosis is very frequently occurred in middle aged and old women.

Therapeutics for osteoporosis, so far, have been developed to inhibit the resorption of bone by inhibiting the action of osteoclast cells. Fracturability by the reduction of bone mass may be not recovered only by inhibiting the resorption of bone. For the ideal treatment of osteoporosis, the recovery from the fracturability, there is necessity that the medicine inhibit the resorption of bone and accelerate the remodeling of bone.

We, inventors have synthesized various compounds and examined their effect of antagonizing LTB-4 receptor and of accelerating the bone formation in order to inhibit and treat the disease relevant to LTB-4 and osteoporosis.

As a result, the present inventors completed the invention through synthesizing 3-amino-1,2-benzoisoxazole derivatives, represented by Formula I, and identifying their effect of antagonizing LTB-4 receptor and of accelerating the bone formation.

Summary of the Invention

The present invention has an object to provide novel 3-amino-1,2-benzoisoxazole derivatives, represented by Formula I.

The present invention has another object to provide process for preparation of 3-amino-1,2-benzoisoxazole derivatives, represented by Formula I.

The present invention has another object to provide pharmaceutical composition containing one of 3-amino-1,2-benzoisoxazole derivatives, represented by Formula I, in effective amount which can antagonize LTB-4 receptor.

Also, the present invention has another object to pharmaceutical composition containing one of 3-amino-1,2-benzoisoxazole derivatives, represented by Formula I, in effective amount which can accelerate the bone formation.

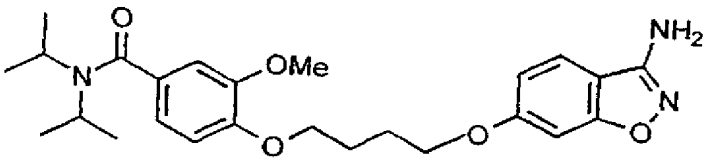
It should be apparent that another purpose of the present invention and their application be made by those skilled in the art from detailed description of the invention.

Detailed Description of the Invention

The present invention will now be described in detail.

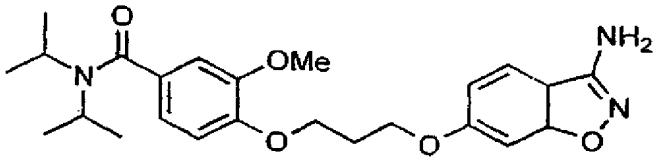
Compounds, represented by Formula I, according to the present invention are N,N-diisopropyl-4-[4-(3-aminobenzo[*d*]isoxazol-6-yloxy)butoxy]-3-methoxybenzamide(HS-1141), represented by Formula II;

Formula II



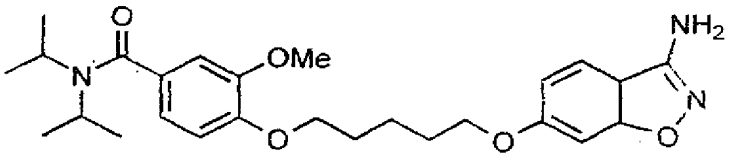
N,N-diisopropyl-4-[3-(3-aminobenzo[*d*]isoxazol-6-yloxy) propoxy]-3-methoxybenzamide(HS-1151), represented by Formula III; and

Formula III



N,N-diisopropyl-4-[5-(3-aminobenzo[*d*]isoxazol-6-yloxy)pentoxy]-3-methoxybenzamide(HS-1132), represented by Formula IV.

Formula IV



As demonstrated by the following Experiment, compounds of Formula II to IV according to the present invention can be utilized as inhibitor and therapeutics for the disease relevant to LTB-4 or osteoporosis, because the compounds have effects of LTB-4 receptor antagonist and of accelerating the bone formation.

Compounds according to the present invention can be administered in effective amount to inhibit the action of LTB-4 receptor or to treat osteoporosis by various administrable path; and the form and dose thereof can be determined by those skilled in the art in consideration of administrative object; administrable path; and status and weight of patient.

LTB-4 receptor antagonist or therapeutics for osteoporosis, preferably, contains both one of 3-amino-1,2-benzoisoxazole derivatives, represented by Formula I, and pharmaceutically acceptable carriers. These carriers can be selected from the group comprising the standard pharmaceutically acceptable carriers, which is commonly used in, pasteurized solution, tablet, coated tablet, and capsule. These carriers, typically, contain bulking agent, such as starch, milk, sugar, specific clay,

gelatin, stearic acid, talc, vegetable fat or oil, gum and glycols, etc. or other kind of known bulking agent. Also, sweetening agent, coloring additives and other component can be contained in the carriers.

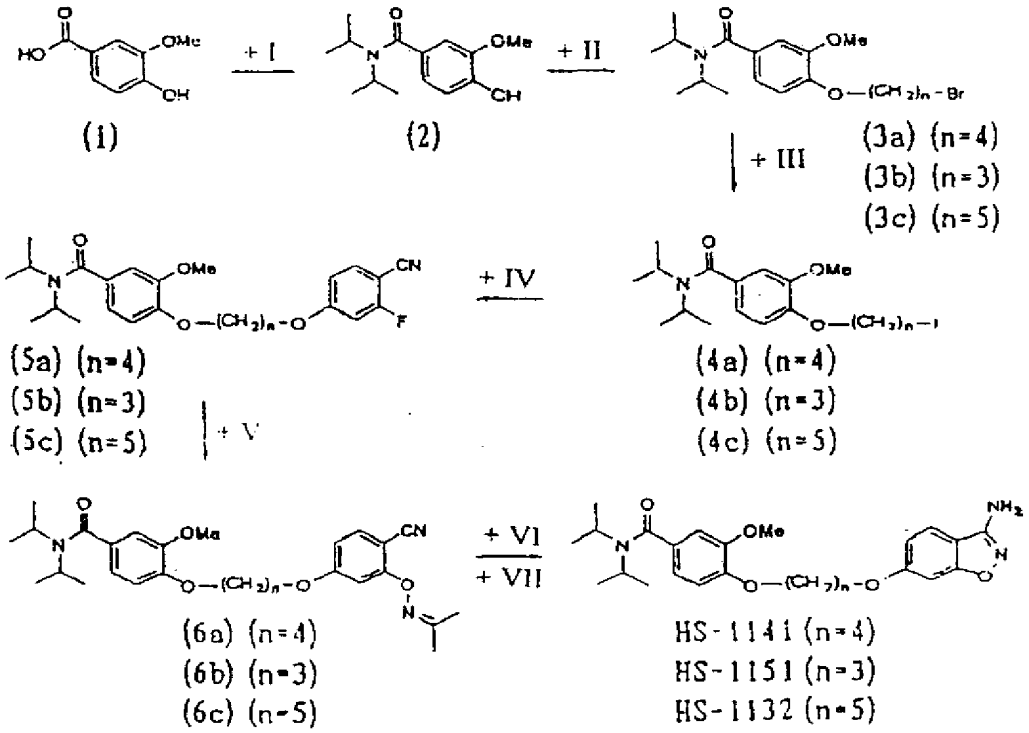
Composition, which contain these carriers, can be formatted by the known method. But, composition, which contain 3-amino-1,2-benzoisoxazole derivatives for LTB-4 receptor antagonist and therapeutics for osteoporosis, has never been reported.

In the present invention, LTB-4 receptor antagonist and therapeutics for osteoporosis containing one of 3-amino-1,2-benzoisoxazole derivatives, can be administered by the known manner, such as oral dose, intravenous, intramuscular, and percutaneous injection, and so on. But it is not limited to these manner.

In carrying out the present invention, 3-amino-1,2-benzo-isoxazole derivatives may be contained in a very extensive range of amount in the pharmaceutical composition. Effective amount of 3-amino-1,2-benzo-isoxazole for LTB-4 receptor antagonist or therapeutics for osteoporosis is 10 - 1000 mg/day. Dose of composition and its frequency can be easily determined by those skilled in the art according to characteristics of administrative form; status and weight of patient; size of inflammatory lesions; path and frequency of administration; and characteristics of specific derivatives to be used.

Process for preparation of compound according to the present invention comprises steps, represented by Scheme I, with the following 4-hydroxy-3-methoxybenzoic acid(1) as starting material, and the specific condition of reaction is shown in the Examples, as follows:

Scheme I



in which I is diisopropylamine;

II is dibromobutane(a), dibromopropane(b) or dibromopentane(c);

III is sodium iodide(NaI);

IV is 2-fluoro-4-hydroxybenzonitrile;

V is acetoneoxime;

VI is hydrochloric acid; and

VII is potassium carbonate(K_2CO_3).

The present invention has been described by reference to specific examples chosen for the purpose of illustration, but it is apparent that the present invention should not be limited by the specific disclosure herein.

The abbreviation used in this specification means, as follows:

DMF : dimethyl formamide

DMSO : dimethyl sulfoxide

GF/C : glass fiber filter type C

HBSS media : Hank's balanced salt solution

TMS : tetramethylsilane (reference material of NMR spectrum)

Compounds according to the present invention was identified by mass spectrum and NMR spectrum using NMR spectrometer(made by Varian Co.) according to the method of Lambert(Lambert *et al.*, *Organic Structural Analysis*, Macmillan Pub. Co., NY, 1993).

<Example 1> Preparation of N,N-diisopropyl-4-[2-isopropylidene nitro oxy-benzonitrile-4-yloxy)butoxy]-3-methoxybenzamide [compound(6a)]

(Step 1) Preparation of N,N-diisopropyl-4-hydroxy-3-methoxybenzamide [compound(2)]

4-Hydroxy-3-methoxybenzoic acid, compound(1), (5 g,

29.6 mmol) was dissolved in methylene chloride(200 ml), then hereto were added thionyl chloride(20 ml, 272 mmol) and DMF(1 ml, 12.8 mmol), refluxed for 1 hour, and concentrated under reduced pressure. The resultant was dissolved in methylene chloride(200 ml), and hereto was added diisopropylamine(20 ml, 142.8 mmol). It was stirred for 2 hours, diluted in ethyl acetate(500 ml), and washed with aqueous solution of hydrochloric acid(100 ml, 1N) for 2 times and saturated aqueous solution of sodium chloride(130 ml). The resultant organic layer was dried over anhydrous magnesium sulfate, and the solvent was removed. Resultant was purified by column chromatography (ethyl acetate : n-hexane = 2:3) to obtain 5.23 g of compound(2) [R_f: 0.32, yield: 70 %].

^{1}H NMR($CDCl_3$, 200 MHz) δ 1.20(d, 12H, J=2.6Hz), 3.69(m, 2H), 3.79(s, 3H), 6.74(m, 3H).

^{13}C NMR($CDCl_3$, 200 MHz) δ 20.5, 47.8, 55.6, 110.1, 115.0, 118.4, 129.9, 147.0, 147.3, 169.8.

(Step 2) Preparation of N,N-diisopropyl-4-hydroxy-3-methoxybenzamide [compound(3a)]

N,N-Diisopropyl-4-hydroxy-3-methoxybenzamide, obtained in the above Step 1, (2.0 g, 7.96 mmol) was dissolved in DMF(30 ml), and hereto was added potassium carbonate(1.32 g, 9.55 mmol). The reaction mixture was stirred for 30 minutes, then hereto was added dibromobutane(1.14 ml, 9.55 mmol), and refluxed for 5 hours.

After diluting the reaction mixture with ethyl acetate(20 ml), it was washed with aqueous solution of hydrochloric acid(1N), aqueous solution of sodium chloride, and distilled water. The organic layer was dried over anhydrous magnesium sulfate, and was removed the solvent. The resultant was purified by column chromatography(ethyl acetate : n-hexane = 1:1) to obtain 1.9 g of compound(3a) [R_f: 0.26, yield: 62 %].

(Step 3) Preparation of N,N-diisopropyl-4-(4-iodobutoxy)-3-methoxybenzamide [compound(4a)]

N,N-Diisopropyl-4-(4-bromobutoxy)-3-methoxybenzamide, obtained by the above Step 2, (1.9 g, 4.92 mmol) was dissolved in acetone(30 ml), and hereto was added sodium iodide(NaI; 1.87 g, 9.84 mmol). The reaction mixture was refluxed for 10 hours, and the solvent was removed. The resultant was dissolved in diethyl ether, and the organic layer was washed with aqueous solution of sodium chloride and distilled water. The organic layer was dried over anhydrous magnesium sulfate, and removed the solvent. The resultant was purified by column chromatography(ethyl acetate : n-hexane = 1:1) to obtain 1.41 g of compound (4a) [R_f: 0.24, yield: 66 %].

(Step 4) Preparation of N,N-diisopropyl-4-[(2-fluorobenzonitrile-4-yloxy)butoxy]-3-methoxybenzamide [compound(5a)]

2-Fluoro-4-hydroxybenzonitrile(0.403 g, 2.98 mmol) was dissolved in DMF(20 ml), then hereto was added sodium hydride(0.16 g, 3.58 mmol) at 0°C, and stirred for 20 minutes. Compound(4a)(1.41 g, 3.28 mmol) was dissolved in DMF(10 ml), and it was added to the above mixture. The reaction mixture was stirred for 2 hours at room temperature, diluted in ethyl acetate(20 ml), and washed with distilled water for 4 times. The organic layer was dried over anhydrous magnesium sulfate, and the solvent was removed. The resultant was purified by column chromatography(ethyl acetate : n-hexane = 1:1) to obtain 0.69 g of compound(5a) [R_f: 0.32, yield: 56 %].

^{1}H NMR($CDCl_3$, 200 MHz) δ 1.25-1.45(m, 12H), 2.00(m, 2H), 3.72(br, 2H), 3.83(s, 3H), 4.09(m, 4H), 6.72(m, 2H), 6.85(d, 2H), 7.48(t, 1H, J=7.8Hz).

^{13}C NMR($CDCl_3$, 200 MHz) δ 20.6, 25.4, 25.7, 48.1, 55.8, 68.4, 92.4, 102.5, 109.9, 111.7, 112.2, 114.3, 118.1, 131.6, 134.0, 148.5, 149.1, 161.8, 164.2, 166.9, 170.6.

(Step 5) Preparation of N,N-diisopropyl-4-[2-isopropylidene nitro oxy-benzonitrile-4-yloxy)butoxy]-3-methoxybenzamide [compound(6a)]

Acetoneoxime(0.52 g, 7.15 mmol) was dissolved in DMF(20 ml), and hereto was added potassium t-butoxide

(0.80 g, 7.15 mmol). The reaction mixture was stirred for 30 minutes, then hereto was added compound(5a)(0.586 g, 1.43 mmol), and stirred for 5 hours. The resultant was poured into the mixed solution of aqueous solution of ammonium chloride and diethyl ether, then the organic layer was separated and washed with distilled water for 3 times. The organic layer was dried over anhydrous magnesium sulfate, and the solvent was removed. The resultant was purified by column chromatography(ethyl acetate : n-hexane = 1:1) to obtain 0.636 g of compound(6a) [R_f: 0.32, yield: 96 %].

^{1}H NMR($CDCl_3$, 200 MHz) δ 1.20-1.45(m, 12H), 2.00-2.10(m, 4H), 2.05(s, 3H), 3.74(br, 2H), 3.86(s, 3H), 4.11(t, 4H, J=5.78Hz), 6.54(dd, 1H, J=2.32Hz, 8.60Hz), 6.86(m, 3H), 7.08(d, 1H, J=2.32Hz), 7.43(d, 1H, J=8.60Hz).

^{13}C NMR($CDCl_3$, 200 MHz) δ 15.9, 20.2, 21.0, 25.1, 25.3, 47.8, 55.4, 67.5, 67.9, 90.2, 100.1, 108.1, 109.5, 112.0, 115.9, 117.8, 131.1, 133.2, 148.3, 148.8, 160.7, 162.0, 163.4, 170.1.

<Example 2> Preparation of N,N-diisopropyl-4-[4-(3-amino-benzo[d]isoxazol-6-yloxy)butoxy]-3-methoxybenzamide (HS-1141)

Compound(6a), obtained by the Example 1, (0.636 g, 1.37 mmol) was added to the mixed solution of ethanol(10 ml) and aqueous solution of hydrochloric acid(5 %, 10 ml), then heated to 50°C and left for 10 hours. The

reaction mixture was concentrated under reduced pressure to remove ethanol, and the resultant aqueous solution was turned into basic with aqueous solution of potassium carbonate. It was extracted with ethyl acetate for 3 times, and the organic layer was washed with distilled water. The organic layer was dried over anhydrous magnesium sulfate, and the solvent was removed. The resultant was purified by column chromatography (ethyl acetate : n-hexane = 1:1) to obtain 0.401 g of desired compound, HS-1141 [R_f: 0.32, yield: 64 %].

^{1}H NMR($CDCl_3$, 200 MHz) δ 1.20-1.50(m, 12H), 2.05(m, 4H), 3.75(br, 2H), 3.85(s, 3H), 4.13(m, 4H), 6.86-6.79(m, 5H), 7.35(d, 1H, J=8.4Hz).

^{13}C NMR($CDCl_3$, 200 MHz) δ 20.7, 25.8, 48.0, 55.8, 67.9, 68.4, 93.3, 109.2, 109.8, 112.1, 118.1, 120.6, 131.4, 148.6, 149.1,157.8, 161.4, 164.7, 170.8.

Here is the result of analysis of HS-1141 by mass spectrum.

Calculated : C(65.62), H(7.71), N(9.18).

Found : C(65.70), H(7.49), N(8.87).

<Example 3> Preparation of N,N-diisopropyl-4-[3-(3-amino-benzo[d]isoxazol-6-yloxy)propoxy]-3-methoxybenzamide (HS-1151)

Compound(3b) was prepared by the same condition of Step 2 in the Example 1, except for replacing dibromo-

butane with dibromo- propane, and from this compound(6b) was prepared by the same condition of Example 1 through the intermediates, compound(3b), (4b), and (5b).

HS-1151 was obtained by the same condition of Example 2, except for replacing compound(6a) with compound(6b) [R_f : 0.26 (ethyl acetate : n-hexane = 1 : 1)].

^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.25-1.91(m, 12H), 2.35(t, 2H), 3.72(br, 2H), 3.86(s, 3H), 4.24(t, 4H, J=5.8Hz), 6.82-6.91(m, 5H), 7.35(d, 1H, J=8.2Hz)

^{13}C NMR($CDCl_3$, 200 MHz) δ 20.7, 28.9, 48.3, 55.8, 64.8, 65.4, 93.6, 109.4, 109.9, 112.6, 112.9, 118.1, 120.6, 131.7, 148.6, 149.2, 157.8, 161.4, 164.6, 170.8

<Example 4> Preparation of N,N-diisopropyl-4-[5-(3-amino-benzo[*d*]isoxazol-6-yloxy)pentoxy]-3-methoxybenzamide (HS-1132)

Compound(3c) was prepared by the same condition of Step 2 in the Example 1, except for replacing dibromo-butane with dibromopentane, and from this compound(6c) was prepared by the same condition of Example 1 through the intermediate, compound (3c), (4c) and (5c).

HS-1132 was obtained by the same condition of Example 2, except for replacing compound(6a) with compound(6c) [R_f : 0.32 (ethyl acetate : n-hexane = 1 : 1)].

^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.34(m, 12H), 1.68(t, 2H),

1.90(m, 4H), 3.72 (br, 2H), 3.84(s, 3H), 4.02(t, 4H, J=6.2Hz), 6.86-6.74(m, 5H), 7.34(d, 1H, J=8.4Hz).

^{13}C NMR ($CDCl_3$, 200 MHz) δ 20.6, 22.4, 28.5, 28.6, 49.1, 55.7, 68.0, 68.5, 93.2, 109.3, 109.8, 112.2, 112.7, 118.1, 120.7. 131.7, 148.7, 149.0, 157.9, 161.4, 164.5, 170.7.

<Experiment 1> Test on antagonizing action for LTB-4 receptor

Antagonizing action of compounds, which are obtained by the above Example 2 to 4, for LTB-4 receptor was measured, as follows:

Neutrophil was separated from whole blood of human by precipitation using "Dextran T-500", and by the inclined centrifugation with Ficoll/Paque (Pharmacia Co.) (Boyum, *Scan. J. Clin. Lab. Invest., 21 suppl. 97*, 77-89, 1989).

Mixed erythrocyte was removed by hemolysis of hypotonic solution. Final neutrophil was dispersed to 3×10^7 cell/ml in HBSS media and used for measuring the antagonizing action for LTB-4 receptor.

Measurement of antagonizing action for LTB-4 was followed by the reported method(Tsai *et al.*, *Prostaglandins*, *38*, 655-674, 1989), and concrete experimental method was mentioned, as follows:

0.5nM of [^3H]-LTB-4(200Ci/mmol), test sample to measure the antagonizing action for LTB-4 receptor, and

cell dispersed in HBSS media was added to 12 mm X 75 mm of polyethylene tube(final volume: 200 μl), and left in ice bath for 45 minutes.

To separate [^{3}H]-LTB-4 bound to neutrophil and isolated [^{3}H]-LTB-4 not bound to neutrophil, the above mixture was filtered through GF/C filter(made by Wattman Co.). Filter paper was washed with pH 7.4 of cold Tris-buffer solution(5 ml) for 3 times, dried, and measured radioactivity. The selective binding of LTB-4 to neutrophil can be detected by the difference between radioactivities without antagonist in case that LTB-4 was totally bound to neutrophil, and that LTB-4 was bound to neutrophil in addition of radioisotope-unlabeled LTB-4 1000 times.

Degree of antagonizing action in Table I is represented as inhibitory degree of selective binding which is % value of samples to the control, and IC_{50} was meant to concentration of 50% of antagonizing in binding to receptor.

To compare the antagonizing action of compounds according to the present invention with that of existing antagonist, CGS-25019C, known compound was used (Morrissey, M. M., and Suh, H., USP 5,451,700; Brooks, C. D. *et al.*, *J. Med. Chem. 39*, 2629-2654, 1996)

Table I

HS compounds	Degree of inhibition(%)			IC_{50}
	10 nM	100 nM	1 μM	
HS-1151	< 10	37	92	
HS-1141	64	95	99	7 nM
HS-1132	< 10	10	90	
CGS-25019C	11	68	97	80 nM

From the above Table I, it would be understood that the effect of antagonizing action of the compound of the present invention for LTB-4 receptor was similar to or better(in case of HS-1141) than the known compound, CGS-25019C.

<Experiment 2> evaluation of bonelike nodule forming

Approximately 30 of calvariae of fetal rat, removed all the tissue, was dissolved in 5 ml sterilized colagenase(0.1%) and trypsin solution (0.05 %) at 37°C. 20 Minutes after dissolving, the released cells were collected, and hereto was added fetal serum to the same amount. This procedure was carried out for 3-6 times in every 20 minutes to collect the isolated cells. Collected cells were separated by centrifugation(400 Xg) for 5 minutes and it was suspended in α-MEM media, containing 10%(v/v) fetal bovine serum. Collected cells were

cultivated in petri dish for 2-3 days, then separated with trypsin, and it were placed in 96 wells to 2.0×10^3 cells/100 μl in each well.

After cultivating the cells for 2-3 days, the media were changed to 5% fetal calf serum, 150 μg/ml ascorbic acid and 5 mM β-glycerophosphate, plus or minus sample(HS-1141). The control was in wells without the sample, and this time was arbitrarily set as day. Activity can be measured by the comparison of number of nodule and area of it relatively, and it was shown in Table II. Formed nodule was analyzed with image analyzer(Biorad Co., USA); camcorder(SONY Co.); and microscope(Leitz Co.).

Table II

Sample	Concentration (M)	Number of nodule (No.)	Area of nodule (mm^2)
The control	-	10.04±1.23	0.12±0.026
HS-1141	10-8	22.80±4.71	0.273±0.019
	10-9	24.00±4.04	0.379±0.068
	10-10	19.40±1.29	0.320±0.082
	10-11	25.67±3.54	0.342±0.065

From the above Table II, it is apparent that remodeling of bonelike nodule was increased in over than

2 times by HS-1141. Therefore, it is understood that HS-1141 stimulate the bone formation effectively.

Meanwhile, test on toxicity to the compounds of this invention was carried out.

Sample, the compounds of this invention, was dissolved in distilled water, and this solution was injected to rats(5/group). Then the death rate was measured by observing for 14 days after injection.

Lethal dose of 50%(LD_{50}) of the compounds of this invention was 1 g/kg.

The compounds of this invention especially accelerate the remodeling of bone in concentration, which is 10,000 times less than concentration of cell toxicity.

Therefore, the compounds of this invention can be therapeutics for osteoporosis as a stimulant of bone formation.

Effects of the Invention

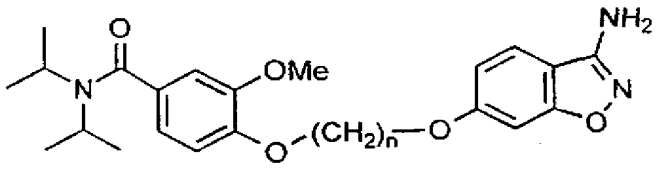
As apparent from the above Experiment, it was found that the compound, represented by Formula I, antagonize LTB-4 receptor and stimulate the bone formation effectively. Therefore, it is expected that good inhibitory and treating effect for the numerous disease relevant to LTB-4 or osteoporosis can be obtained through containing the compound of this invention.

The compounds of this invention can especially stimulate the formation of bonelike nodule, so it can be usefully utilized as therapeutics for osteoporosis.

What is claimed is

1. 3-Amino-1,2-benzoisoxazole derivatives, represented by Formula I, as follows:

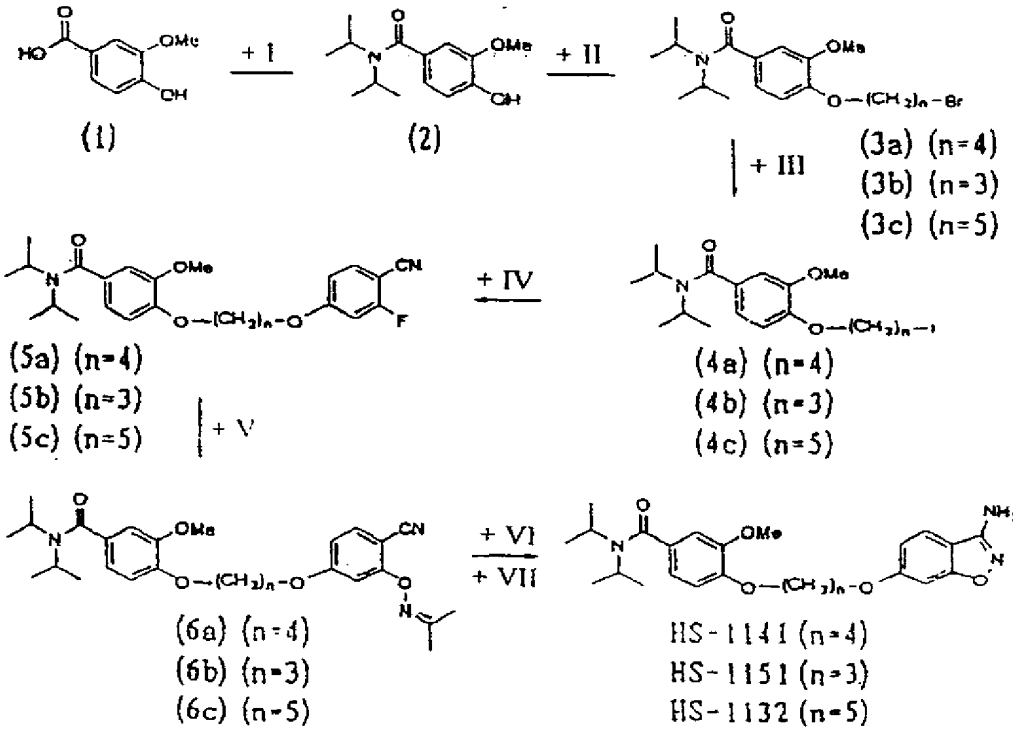
Formula I



(in which, n is integer of 3-5.)

2. Process for preparation of 3-amino-1,2-benzoisoxazole derivatives, represented by Scheme I, as follows:

Scheme I



in which, I is diisopropylamine;

II is dibromobutane(a), dibromopropane(b) or dibromopentane(c);

III is sodium iodide(NaI);

IV is 2-fluoro-4-hydroxybenzonitrile;

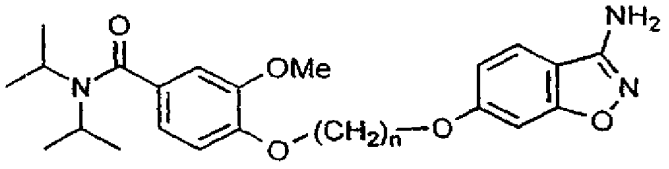
V is acetoneoxime;

VI is hydrochloric acid; and

VII is potassium carbonate(K_2CO_3).

3. LTB-4 receptor antagonist containing one of 3-amino-1,2-benzoisoxazole derivatives, represented by Formula I, in effective amount.

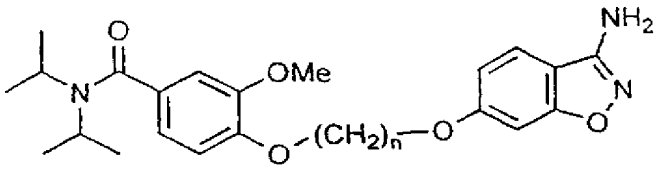
Formula I



4. LTB-4 receptor antagonist as claimed in Cliam 3, wherein one of 3-amino-1,2-benzoisoxazole derivatives is N,N-diisopropyl-4-[4-(3-amino-benzo[*d*]isoxazol-6-yloxy) butoxy]-3-methoxy-benzamide (HS-1141).

5. Therapeutics for osteoporosis containing one of 3-amino-1,2-benzoisoxazol derivatives, represented by Formula I, in effective amount.

Formula I



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6. Therapeutica for osteoporosis as claimed in Claim 5, wherein one of 3-amino-1,2-benzoisoxazol derivatives is N,N-diisopropyl-4-[4-(3-amino-benzo[*d*]isoxazol-6-yloxy)butoxy]-3-methoxy-benzamide (HS-1141).

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR 98/00023

A. CLASSIFICATION OF SUBJECT MATTER

IPC^6: C 07 D 261/20; A 61 K 31/41

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC^6: C 07 D 261/20

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

AT, Chem. Abstr.

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Questel: CAS, WPIL

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	Chemical Abstracts, Vol.126, No.19, 12 May 1997 (Columbus, Ohio, USA), page 554, column 2, abstract No.251094y, SUH, H. et al.:"3-Amino-1,2-benzisoxazoles: a new family of potent inhibitors of LTB_4 binding to the human neutrophils", & Bioorg. Med. Chem. Lett. 1997, 7(4), 389-392 (Eng).	1-6
A	Patent Abstract of Japan, Vol.96, No.21, 1996, JP 08-143525 A (BANYU PHARMACEUT CO., LTD.).	1-6
A	WO 95/13 814 A1 (JANSSEN PHARM.) 26 May 1995 (26.05.95), claim 1; page 3, lines 32ff.	1
A	Patent Abstract of Japan, Vol.6, No.94, 1982, JP 57-26662 (DAINIPPON SEIYAKU).	1
A	EP 0 048 162 A1 (ELI LILLY & CO.) 24 March 1982 (24.03.82), pages 12,13.	1

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
01 April 1998 (01.04.98)	15 April 1998 (15.04.98)

Name and mailing address of the ISA/ AT	Authorized officer
AUSTRIAN PATENT OFFICE Kohlmarkt 8-10 A-1014 Vienna	Hammer
Facsimile No. 1/53424/535	Telephone No. 1/53424/374

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INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/KR 98/00023

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		NO A0 962040	20-05-96
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